REMARKS

This paper is submitted in response to the Office Action mailed March 22, 2004. Following this amendment, Claims 1, 4-20, 22-31, 47-49, and 51-53 are pending. Claims 1, 4, 5, 6, 7, 8, 9, 13, 47, 48, and 49 have been amended, as discussed below. Claims 51-53 have been added. Claims 47-49 have also been amended in accordance with U.S. patent practice. No new matter has been introduced by the amendment to the claims. Applicants reserve the right to pursue any cancelled subject matter in divisional, continuation or continuation-in-part applications.

Claim Objections

Claim 22 has been objected to under 37 C.F.R. 1.75 (c) as being in improper dependent form for failing to further limit the subject matter of a previous claim. Claim 22 depends from claim 14, which is directed to the human TNF-α gene. The Examiner alleges that claim 22 is directed to inserting a cis-acting element into the intron of human TNF-α and that the human TNF-α gene already has a cis-acting nucleotide in an exon (3'UTR) of the gene, but not in an intron. The Examiner further alleges that if the cis-acting element is inserted into an intron of the human TNF-α gene, then it is no longer the human TNF-α gene. The Examiner, therefore concludes that the subject matter of claim 22 is outside of the scope of claim 14 and does not further limit the subject matter of claim 14.

Claim 14 is directed to a DNA construct comprising the TNF-α gene and a *cis*-acting nucleotide sequence, wherein the nucleotide sequence is contained within an intron of the TNF-α gene. Claim 22, dependent on claim 14, merely recites the name of a specific DNA

construct. The *cis*-acting sequence of the invention is inserted in the intron of the TNF-α gene. Therefore, the TNF-α gene in the construct comprises a *cis*-acting nucleotide sequence, within an intron of the gene.

As shown in Example 10 (*see* page 38 of the specification), the *cis*-acting element of the invention is a portable element, which confers splicing control. However, upon transport into the cytoplasm, localized activation of PKR by the *cis*-acting sequence of the invention, residing in resulting mature mRNA is expected to reduce the translation efficiency of the resulting mRNA, through local activation of PKR and phosphorylation of the eIF2α subunit in the cytoplasm. The advantage gained from control of splicing by the *cis*-acting nucleotide sequence of the invention, may be offset by a loss in translation efficiency. A solution to this problem, was provided by the inventors by inserting the *cis*-acting nucleotide sequence of the invention into the intron of the gene of interest. Thus, after first leading to mRNA splicing, the *cis*-acting element (which was inserted to the intron of the gene of interest), is spliced out of the mRNA together with the remainder of the intron, yielding a *cis*-acting free mRNA that will undergo more active translation. Thus, the effect of the cis-acting sequence will be restricted to the nucleus, by its intronic insertion, and in this way, regulation of splicing may be uncoupled from translation control. An illustrative example of such self-elimination of splicing control element is the construct pTNF-a(Δ3'UTR-i3EP). As indicated in the specification, this construct is devoid of the 3'UTR, and therefore lacking the exonic 2-APRE. The *cis*-acting sequence was inserted into the intron of said construct, and thus, this construct exemplifies the feasibility of using the *cis*-acting element of the invention even in an intron of a gene of interest.

Without conceding to the correctness of the Examiner's objection, Applicants have amended claim 13 by replacing "contained" with "inserted." This change alters the claim

into a "product by process" claim, highlighting the step where the *cis*-acting nucleotide sequence is inserted into the intron of the gene of interest, TNF-α. As claimed, the construct is prepared with an intact gene, *i.e.* TNF-α into which the *cis*-acting nucleotide sequence is inserted. Therefore, the Examiner's concern regarding the intact human TNF-α gene is obviated. Support for the amendment can be found in the specification at page 20, line 10-11. Therefore, Applicants respectfully request withdrawal of the objection to claim 22.

The Examiner further objects to claims 47-49 under 37 C.F.R 175(c) as being in improper form, because a multiple dependent claim cannot depend from another multiple dependent claim. New claims 51-53 have been added to remove the multiple dependency. Applicants respectfully request withdrawal of the objection to claims 47-49.

Rejections Under 35 U.S.C. § 112

The Examiner has rejected claims 1, 4-20, and 23-31 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention.

The Examiner contends that these claims are readable on a genus of a *cis*-acting nucleotide sequence, which is capable of rendering the removal of introns from a precursor transcript encoded by a gene, but not allegedly claimed in a specific biochemical or molecule structure that could be envisioned by one skilled in the art at the time of the invention. The Examiner states that the specification does not provide an adequate written description of a representative number of species of *cis*-acting nucleotide sequence. The Examiner thus states

that the disclosure provides sufficient support only for SEQ ID NO: 1 and 2, but not for the genus of *cis*-acting nucleotide sequences.

In the Office Action mailed March 22, 2004, the Examiner reaffirms his contention that the as-filed specification does not provide an adequate description of a representative number of species as embraced by the claimed genus of *cis*-acting nucleotide sequence. More specifically, the Examiner alleges that a mere statement asserting that any sequence with biological functional fragments, derivatives, mutants and homologues of the nucleotide sequence of SEQ ID NO: 1 or 2, without providing the essential and specific description of a representative member of species, does not lend evidentiary support for a skilled artisan to have recognized that the applicants were in possession of the genus of *cis*-acting nucleotide sequence as claimed. The Examiner indicates that Applicants arguments filed on January 15, 2004, have been fully considered, but are not persuasive, because the specification does not provide sufficient description of a genus of *cis*-acting nucleotide sequence consisting of biologically functional fragments, derivatives, mutants and homologues. The Examiner has acknowledged that the prior amendments to claims 1-7 are sufficient in overcoming the written description rejection.

The Examiner further indicates that in view of the In re Wands Factors, the claimed invention is only enabled for *cis*-acting nucleotide sequence set forth in SEQ ID NO: 1 and 2 and is not enabled for the full breadth of the claimed invention. The claimed invention is broader (biologically functional fragments, derivatives, mutants and homologues of that nucleotide sequence of SEQ ID NO: 1 and 2) than the enabling disclosure. The Examiner therefore concludes (on page 10 of the Office Action) that the claimed invention is only enabled for the *cis*-acting sequence set forth in SEQ ID NO:1 or SEQ ID NO: 2.

The Examiner further alleges that the as-filed specification teaches that the *cis*-acting element in the human TNF-α 3'UTR renders the splicing of TNF-α mRNA sensitive to 2-AP and contemplates that this is a unique and novel tool for bringing the expression of a desired gene under the control of this mechanism. The Examine further contends that the state of the art exemplified by Jarrous et al., (page 2820, column 1, lines 5-24) teaches a method of regulating gene expression at the mRNA level transforming a host cell with a vector comprising the TNF-α gene, including the 3'UTR, wherein the activity of the RNA activated eIF2α kinase in the host cells is modulated by the use of 2-AP. It should be noted that, contrary to the Examiner's indication, this cited passage in Jarrous et al., describes 2-AP and its effect on splicing, but however, does not disclose any indication relating to the RNA activated eIF2α kinase.

The Examiner further states that Jarrous et al., further teaches that "Most likely, regulation by 2-AP is mediated by a particular sequence within the TNF-α primary transcript to produce general inhibition of the splicing of this transcript" (page 2821 column 1, lines 38-40). Deletion of a particular sequence from the TNF-α gene renders splicing of the encoded transcript resistant to inhibition by 2-AP, while introduction of said sequence into the TNF-β shifts inhibitory effect of 2-AP from transcription to splicing (page 2821). The Examiner further indicates that the as-filed specification locates the specific sequence that Jarrous et al. speculate, through genetic techniques.

In response, Applicants have amended claims 1, 4, 5, 7-9 to delete the phrase "biologically functional fragments, derivatives, mutants and homologues of SEQ ID NO: 1 and 2." Since the Examiner has acknowledged that the specification provides sufficient disclosure for SEQ ID NOS: 1 and 2, Applicants submit that these amendments are sufficient to overcome

the rejection and respectfully request withdrawal of the rejection of claims 1, 4-20, and 23-31 under 35 U.S.C. 112, first paragraph.

Rejections Under 35 U.S.C. § 102(b)

The Examiner has maintained the rejection of claims 1 and 4-6 under 35 U.S.C. 102 (b) as being anticipated by Adams et al. (Genbank Accession No. T29839). The Examiner alleges that Adams discloses a nucleotide sequence with 99% identity to SEQ ID NO: 1 and 100% identity to SEQ ID NO:2. The Examiner further alleges that the claims do not exclude the nucleotide sequence taught by Adams, and that the applicants have not provided factual evidence that the TNF-α used by Adams et al., does not encode a 3'UTR. The Examiner further indicates that for the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be considered as equivalent to "comprising."

In response and without conceding to the Examiner's arguments, Applicants have amended claims 1, 4, 5 and 7-9 by replacing "consisting essentially of" with the closed transitional phrase, "consisting of." Therefore, claim 1, as amended, excludes nucleotides not recited in SEQ ID NO:1, *i.e.* specific fragment encompassing nucleotides 1069-1173 of the human TNFα gene, or SEQ ID NO:2, *i.e.* specific fragment encompassing nucleotides 1073-1116 of the human TNFα gene. Adams discloses the nucleotide sequence of a 248 base pair fragment of the human TNFα gene and includes sequences that are additional and not a component of the present invention.

The Examiner has also maintained the rejection of claims 7-9, 11, 13, 14, 23, 24, 25 and 27-31, and in addition, claim 10, under 35 U.S.C. 102 (b) as being anticipated by Jarrous et al. The Examiner contends that Jarrous et al. discloses a vector comprising the TNF-α gene including the 3' untranslated region, which reads on a *cis*-acting nucleotide sequence of the present application, and further teaches that the trans-acting factor for the sequence is PKR.

First of all, contrary to the Examiner's stated conclusion that Jarrous et al. teaches that "the trans-acting factor for the sequence is PKR", it does not show any functional connection between a particular sequence and the RNA-activated eIF2α and the RNA-activated eIF2α kinases, or specifically, PKR.

Moreover, although sensitivity to 2-AP is an outstanding property of eIF2α kinases, it is also observed for a number of other, less well-characterized kinases, albeit to a lesser extent. Therefore, the observation of Jarrous et al. that splicing of TNF-α mRNA is sensitive to 2-AP does not provide any guidance for one of skill in the art to determine the nature of the possible step that might be inhibited, or whether the process required an eIF2α kinase, another protein kinase, or no kinase at all. Additional knowledge on the mechanism of PKR activation by 2-APRE and analysis of the effect of wild type and mutant forms of PKR on TNF-α mRNA splicing in cells were needed to demonstrate the involvement of PKR and 2-APRE, as the inventors have performed in support of the present application.

Uniquely among the eIF2α kinases, PKR requires RNA for its activation. Prior to the invention, it was generally accepted by the skilled artisan that linear, double-stranded RNA was required for activation. The finding that the single-stranded and only partially folded 2-APRE does not fulfill the criteria of a typical double-stranded RNA strongly argues for the novelty of activation of PKR by this element.

Thus, Jarrous et al., although indicating that 2-AP is an inhibitor of PKR and heme kinases, and that splicing of TNF-α is inhibited by 2-AP, does not describe or show the existence of a particular *cis*-acting sequence which specifically responds to a particular trans-acting factor which is the PKR.

The Examiner further alleges that the claims read on the vector taught by Jarrous et al., and that the claims do not exclude the vector taught by Jarrous et al. The Examiner further asserts that the applicants have not provided factual evidence that the human TNF-α gene used by Jarrous et al., does not encodes a 3'UTR. The Examiner recites the MPEP § 2112, which states that the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. Therefore, the Examiner asserts that the presently claimed invention does not exclude the vector taught by Jarrous et al., In addition, the Examiner further indicates that for the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be considered as equivalent to "comprising."

As discussed above, Applicants have amended claims 1, 4, 5 and 7-9 by replacing "consisting essentially of" with the closed transitional phrase, "consisting of." Therefore, nucleotides not recited in SEQ ID NO:1 or SEQ ID NO:2 are excluded from the scope of the presently claimed invention. Therefore, Applicants submit that Jarrous et al. do not anticipate the subject matter of claims 7-9, 10, 11, 13, 14, 23, 24, 25 and 27-31.

For the foregoing reasons, Applicants respectfully request withdrawal of the rejection of claims 1, 4-6, 7-9, 10, 11, 13, 14, 21, 23, 24, 25 and 27-31 under 35 U.S.C. 102 (b).

CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully requests withdrawal of the outstanding rejections and allowance of the pending claims.

Applicants have enclosed the fee for a two-month extension of time as required under 37 C.F.R. §1.17(a)(2). Applicants do not believe that any additional fee is required for this filing. Nevertheless, the Commissioner is hereby authorized to charge any fees required for this submission not otherwise enclosed herewith to Deposit Account No. 02-4377. Two copies of this page are enclosed.

Respectfully submitted,

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